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REVIEW

Neurobiologic Processes in Drug Reward and Addiction

Bryon Adinoff, MD

Neurophysiologic processes underlie the uncontrolled, compulsive behaviors defining the addicted state. These “hard-wired” changes in the brain are considered critical for the transition from casual to addictive drug use. This review of preclinical and clinical (primarily neuroimaging) studies will describe how the delineation between pleasure, reward, and addiction has evolved as our understanding of the biologic mechanisms underlying these processes has progressed. Although the mesolimbic dopaminergic efflux associated with drug reward was previously considered the biologic equivalent of pleasure, dopaminergic activation occurs in the presence of unexpected and novel stimuli (either pleasurable or aversive) and appears to determine the motivational state of wanting or expectation. The persistent release of dopamine during chronic drug use progressively recruits limbic brain regions and the prefrontal cortex, embedding drug cues into the amygdala (through glutaminergic mechanisms) and involving the amygdala, anterior cingulate, orbitofrontal cortex, and dorsolateral prefrontal cortex in the obsessive craving for drugs. The abstinent, addicted brain is subsequently primed to return to drug use when triggered by a single use of drug, contextual drug cues, craving, or stress, with each process defined by a relatively distinct brain region or neural pathway. The compulsive drive toward drug use is complemented by deficits in impulse control and decision making, which are also mediated by the orbitofrontal cortex and anterior cingulate. Within this framework, future targets for pharmacologic treatment are suggested. (HARV REV PSYCHIATRY 2004;12:305–320.)

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Rewards are pleasurable. Addictions hurt. Reward is experienced in response to discrete stimuli, providing enjoy-

From the Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas, and VA North Texas Health Care System, Dallas, TX.

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Correspondence: Bryon Adinoff, MD, 116A5, Dallas VAMC, 4500 S. Lancaster Road, Dallas, TX 75216. Email: bryon.adinoff@utsouthwestern.edu

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ment and arousal. Addictions involve persistent, compulsive, and uncontrolled behaviors that are both maladaptive and destructive. Despite these obvious differences, reward and addiction were previously thought to share common neurobiologic underpinnings. This unified model has undergone a dramatic revision, and reward and addiction are now conceptualized as distinct neurochemical processes involving different, albeit overlapping, neuroanatomical circuits. In this review, I will begin with a historical perspective of mesolimbic dopamine and reward, followed by two theories of addiction (i.e., dopamine depletion and sensitization) that have guided medication development for several years. Newer interpretations of dopamine's role in reward and addiction are then presented, reflecting our present understanding of dopamine as mediator of expectation, wanting, and novelty. Two general mechanisms involved in drug relapse will then be discussed: compulsive drive states, considered as four brain regions/pathways, each mediating a distinct relapse trigger (i.e., priming, drug cues, craving, and stress); and the inhibitory dyscontrol that can exacerbate

the compulsive drug drive. The role of mesocorticolimbic dopaminergic and glutaminergic pathways, intracellular mechanisms, and relevant brain regions in compulsive drug drive and inhibitory dyscontrol will be the focus of these sections on drug relapse.

A few caveats are warranted. First, I will often use the term “addiction”¹ (using terminology recommended by the American Academy of Pain Medicine, American Pain Society, and American Society of Addiction Medicine) rather than “dependence”² to refer to the complex of behaviors that include withdrawal, tolerance, loss of control, compulsive use, and continued use despite adverse consequences. Second, addiction will be discussed specifically as it relates to substances of abuse, primarily cocaine. However, the neurobiology, brain structures, and behavioral and cognitive processes involved in the addictive use of substances most likely relate to nonsubstance addictions, such as those involving sex and gambling. Third, any review of neurobiological processes in addiction must, by necessity, be selective in its approach and regretfully omit important advances in the field. Last, this review will focus upon the biologic processes involved in the return to substance use after a period of abstinence—processes that pose, I believe, the most interesting and perplexing questions in understanding the nature of addiction. Thus, theories of addiction involving “opponent” or withdrawal processes will not be discussed.^{3–5}

REWARD AND MESOLIMBIC DOPAMINE

Olds and Milner⁶ initiated our modern understanding of brain reward mechanisms in 1954. In this seminal work, rodents were given the opportunity to administer electrical stimulation to various brain regions. Specific brain areas were found to elicit persistent self-stimulation, often to the exclusion of any other behaviors. Confirming in humans the results of Olds and Milner, Heath^{7,8} demonstrated that subjects would similarly self-administer electrical stimuli to specific “pleasure” areas of the brain (for ethical commentary, see Baumeister’s 2000 article).⁹ Over the subsequent decades, the brain structures, neuronal pathways, and relevant neurotransmitters implicated in the experience of reward and reinforcement were further refined (see review by Gardner).¹⁰ The mesolimbic pathway, in particular, was identified as the key component in reward assessment. This pathway originates with dopaminergic cell bodies in the ventral tegmental area (VTA), a dopamine-rich nucleus located in the ventral portion (or tegmentum, meaning “covering”) of the midbrain. These dopaminergic axons project and primarily terminate in the nucleus accumbens (NAc) in the ventral striatum, but also extend into the amygdala, bed nucleus of stria terminalis (BNST), lateral septal area, and lateral hypothalamus. The VTA is in close proximity to the substantia nigra, another dopamine-rich nucleus. Whereas the substantia nigra projects primarily to the dorsal striatum

(via the mesostriatal pathway) and mediates motor activity, the mesolimbic pathway mediates reward.¹¹

The experience of reward is accompanied by activation of the mesolimbic dopaminergic pathway. Natural rewards, such as food or sex—as well as most substances that are abused by humans, including alcohol, amphetamine, caffeine, cocaine, marijuana, nicotine, opiates, and phencyclidine^{10,12–17}—increase extracellular concentrations of mesolimbic dopamine (DA). The stimulants cocaine and amphetamine directly amplify the mesolimbic dopaminergic signal at the postsynaptic DA receptor through different synaptic mechanisms. Cocaine increases synaptic dopaminergic concentrations by blocking the presynaptic dopamine transporter (DAT).¹⁸ The DAT is responsible for reabsorbing synaptic DA back into the presynaptic neuron, and occupancy of the DAT by cocaine prevents DA reuptake. The amphetamines increase synaptic DA primarily by increasing DA release from the synaptic vesicles.¹⁹ Both cocaine and the amphetamines increase both the absolute concentration of DA in the synapse and the time interval that DA remains at the postsynaptic receptor site. Due to their direct effect upon dopaminergic activity, the stimulants (particularly cocaine) are considered prototypic drugs of reward and have thus become the focus of biological and treatment studies (see following sections). Although nonstimulant drugs indirectly interact with the mesolimbic pathways through a variety of receptor systems, these compounds share the common pharmacologic property of stimulating mesolimbic DA—primarily in the NAc.¹⁰ These nonstimulant drugs bind with either G protein-coupled or ligand-gated ion channel receptors. Drugs that bind with G protein-coupled receptors (and their respective binding site(s)), include tetrahydrocannabinol (THC) (an agonist at cannabinoid receptors); opiates, such as heroin or morphine (agonists at opioid receptors, activating dopamine via VTA GABAergic disinhibition);²⁰ and caffeine (an antagonist at striatal adenosine A2 receptors). Drugs that bind with ligand-gated ion channel receptors include alcohol (an allostatic facilitator at the GABAergic receptors and inhibitor of N-methyl-D-aspartate [NMDA] glutamate receptors); phencyclidine (PCP) (blocks NMDA glutamate receptors); and nicotine products, such as cigarettes (agonists at nicotinic cholinergic receptors).

The anatomical distinction made between drug reward and drug withdrawal further confirmed the importance of the mesolimbic pathway in drug self-administration. In a classic study by Bozarth and Wise,²¹ morphine was administered into either the VTA or periventricular gray (PVG) region of rats for 72 hours (the PVG is a brain stem region containing a high concentration of opioid receptors). Following the administration of the opioid antagonist naloxone, PVG morphine-infused rats showed signs of withdrawal, whereas VTA morphine-infused rats did not. Furthermore, rats could be trained to self-administer morphine into the VTA but not

the PVG. This study demonstrated a clear separation between the biological processes involved in withdrawal versus reward, further supporting the role of the VTA in drug reward.

A wealth of preclinical studies has directly examined the effects of increasing or decreasing DA in the NAc upon drug self-administration.^{22–24} Using an *in vivo* “microdialysis” technique, minute changes in extracellular neurotransmitter concentrations can be assessed in real time during experimental manipulations. With this technique, Pettit and Justice²⁵ found a correlation between the amount of cocaine self-administered by rodents and the extracellular DA released in the NAc. Conversely, an attenuation of the self-administration of stimulants follows either the administration of DA antagonists (e.g., haloperidol)^{26,27} or the neurotoxic lesioning of the dopaminergic cells in the NAc.²⁸ Functional neuroimaging studies have further confirmed the relevance of the mesolimbic pathway and DA release to the cocaine-induced high. Using functional magnetic resonance imaging (fMRI), Breiter and colleagues²⁹ administered cocaine to cocaine-addicted subjects while their brains were being scanned. Over the next several minutes, subjects were able to distinguish the “rush” that they reported during the first minute or two following cocaine use from the “craving” experienced following dissipation of the rush. Since fMRI techniques allow measures of regional brain activation to be assessed every few seconds, distinct images of brain activity were obtained during both the “rush” and “craving” experiences. During the rush, but not craving, increased brain activation was observed in the VTA, consistent with activation of the mesolimbic pathway. In a study using positron emission tomography (PET), Volkow and colleagues³⁰ administered cocaine to subjects during imaging, and reported that the level of DAT occupancy or DAT blockade was significantly associated with the magnitude of self-reported high. Additional studies by Volkow and colleagues³¹ further suggest that the release of DA (as assessed by D2 receptor occupation) was a better predictor of high intensity than was DAT blockade. A general assumption guiding addiction research for much of the past two decades has therefore been that the addictive effects of the primary substances of abuse were contingent upon dopaminergic activation of the mesolimbic pathway.

THE TRANSITION FROM REWARD TO ADDICTION: A FOCUS ON DOPAMINE

The Dopamine Depletion Hypothesis of Addiction

The high or rush associated with the mesolimbic activation suggested that the neurotransmitter DA was itself responsible for the pleasurable feelings associated with rewards. The drive for continued drug administration (that is, addictive

behaviors) was considered a consequence of the continued need to elicit heightened DA concentrations—and the resultant pleasure—in the mesolimbic pathway and associated brain regions. This hypothesis further predicted that the binge use of cocaine would result in a DA deficit state,^{3,32,33} resulting in a cocaine crash (i.e., anhedonia, depression) and a biologic demand (i.e., craving) for more cocaine to replenish the depleted DA stores. Drug-induced DA depletion has been variously referred to as the “dopamine depletion hypothesis”³² or the “general anhedonia model.”³⁴ Evidence of increased striatal DAT receptors³⁵ (suggesting upregulation in response to persistent DAT occupancy by cocaine) and decreased DA D2 receptors^{36,37} (suggesting downregulation in response to persistently elevated DA concentrations at the postsynaptic site) by PET imaging studies further supported dysregulation of the dopaminergic system. The attenuated D2 striatal concentrations were hypothesized to lessen the reinforcing salience of natural rewards and to heighten the need for substance-induced elevations in dopaminergic efflux. For example, an increase in D2 receptors decreases alcohol self-administration in rodents,³⁸ whereas primates with lower D2 receptors demonstrate higher rates of cocaine self-administration.³⁹ Cocaine-dependent subjects also demonstrated significantly reduced dopaminergic cell activity (as evidenced by reduced changes in striatal [¹¹C]raclopride binding) following methylphenidate infusion relative to controls, as well as diminished reports of feeling “high.” Extracellular DA concentrations in the NAc were also reported to be inversely correlated with cocaine self-administration in rats, such that low DA levels produced moderate to high self-administration rates, and high DA levels produced moderate to low self-administration rates.⁴⁰

To date, attempts to treat cocaine addiction by activating dopaminergic receptors—and thereby increasing dopaminergic tone—have not been successful. A number of dopaminergic agonists (e.g., pergolide,⁴¹ amantadine,^{42,43} bromocriptine,^{42,44,45} methylphenidate,⁴⁶ and mazindol)⁴⁷ did not attenuate relapse rates in cocaine-addicted subjects. Especially puzzling was a preclinical study exploring ventral striatal DA release and cocaine self-administration in DAT-deficient mice. Rocha and colleagues⁴⁸ studied genetically altered mice in which the DAT receptor was not expressed (DAT $-/-$ knockout mice). Since these mice did not have a DAT receptor to bind cocaine, cocaine administration did not induce an extracellular increase in ventral striatal DA. Unexpectedly, however, the DAT $-/-$ mice self-administered similar amounts of cocaine as the wild-type mice (mice with intact DAT receptors). This finding revealed that neither the DAT nor an increase in synaptic DA was essential for the self-administration of cocaine. Additional studies by Rocha and colleagues⁴⁸ (reported in the same article) suggested that the reinforcement properties of cocaine may have been mediated by cocaine’s occupancy of the serotonergic

reuptake transporter. Other investigations, as reviewed by Spanagel and Weiss,⁴⁹ also suggested that, except for the stimulants, mesolimbic DA neurotransmission does not play a crucial role in reinforcement maintained by drug of abuse.

Sensitization and Addiction

The sensitization hypothesis posited a contrasting view of dopamine's relevance to the addictive process. This hypothesis predicted that the repeated administration of drugs would "sensitize" the DA system to the drug and the associated drug cues.^{50–52} This phenomenon was predicated upon observations that the intermittent, recurrent application of electrical stimuli to limbic brain regions induces a progressively excitable neuronal locus. The sensitized locus then exhibits a persistent, heightened sensitivity to the subsequent application of the original stimulus or its associated cues.^{53,54} Cocaine-induced sensitization was first observed by Grode in 1912,⁵⁵ which was followed by pre-clinical studies showing both a progressive development in the likelihood of generalized seizures following daily cocaine administration⁵¹ and heightened sensitivity of dopaminergic receptors to psychomotor stimulants.^{56–58} Cocaine-induced limbic sensitization was suggested as a causal link between chronic cocaine use and cocaine-induced seizures,⁵⁹ panic attacks,^{60,61} psychosis,⁶² and craving.⁵⁰ The sensitization hypothesis of addiction (particularly with regard to cocaine) therefore predicted that relapse to drug use would decrease in response either to drugs used to suppress neuronal hyperexcitability (e.g., carbamazepine for temporal lobe epilepsy) or to dopaminergic antagonists that antagonize the hypersensitive dopaminergic response. Double-blind, placebo-controlled studies of carbamazepine demonstrated limited efficacy in the treatment of cocaine dependence,^{63–65} however, and dopaminergic antagonists (e.g., flupenthixol, risperidone, and ecopipam) were ineffective in decreasing relapse to cocaine use.⁶⁶

Pharmacologic interventions guided by the DA-depletion or -sensitization hypotheses did not generate useful medications for the treatment of cocaine addiction. These clinical trials suggested that disruptions in dopaminergic transmission were subtler than simply an increase or decrease in extracellular release or dopaminergic sensitivity. A reevaluation of dopamine's role in addictive disorders was therefore warranted.

INCENTIVE SALIENCE, LEARNING, AND NOVELTY: A RECONSIDERATION OF MESOLIMBIC DOPAMINE

In addition to the disappointing clinical response to dopaminergic agonists and antagonists, a paradigm shift in the role of DA in the addictive process occurred with

the recognition that (1) DA does not, in and of itself, induce "pleasure," (2) mesolimbic DA efflux increases not only in response to a reward, but also in anticipation of a potential reward and during aversive states, including foot shock, restraint stress, and the administration of anxiogenic drugs,^{17,24,34} (3) extracellular increases in accumbens DA are attenuated in rodents self-administering cocaine relative to "yoked" littermates (rodents that passively receive the same amount of cocaine that the other rodents self-administer),⁶⁷ revealing that the self-administration of cocaine elicits less mesolimbic DA efflux compared to the passive administration of cocaine, and (4) DA plays critical, and overlapping, roles in the interpretation of stimuli and the acquisition of behaviors reinforced by natural rewards and drug stimuli.

Thus, the initial assumptions regarding the role of electrical brain stimulation in defining "reward" pathways were apparently overly simplistic. Berridge⁶⁸ astutely noted that the early work of Heath^{7,8} (see above) reported that patients compulsively administered electrical stimuli. Rather than endorsing "pleasure" from the experience, however, these patients described a desire for more stimulation and other hedonic pursuits. It appeared that the "pleasure" pathway, identified primarily from studies of animals (who are notoriously reluctant to share their true mood states), may have been mislabeled. Instead, Berridge and colleagues²³ and others⁶⁹ have suggested that the mesolimbic pathway determines the *incentive salience*, or *wanting*, of a prospective reward—not the pleasurable experience of the reward itself. Stimulation of this pathway would therefore result in the motivational state of "wanting" (an *expectation* of pleasure) but would not mediate the reward's hedonic, affective state, or "liking."⁷⁰ The distinction between "liking" and "wanting" was critical, as it segregated the euphorogenic power of a substance from its addictive potential. In fact, previous studies have revealed that the drug self-administration could be maintained in the addicted subject in the absence of subjective pleasure—that is, drug liking was not a prerequisite for drug-seeking and drug-taking behavior.⁷¹ Di Chiara¹⁵ theorized a somewhat similar, though distinctive, role of the NAc, positing that mesolimbic dopaminergic activation affects *motivational learning*, not salience (see next section). Schulz and colleagues⁷² demonstrated that DA neurons fire only in response to novel rewards, regardless of the stimulus's hedonic value; activation of the signal was dependent upon the predictability of the reward. Thus, an unexpected, novel, salient, and arousing stimulus elicits a strong dopaminergic signal, regardless of the motivational valence of the stimulus.⁷³ With each repeated presentation of the stimulus, DA discharge lessens until the stimulus no longer produces a neuronal response. This role of DA is consistent with PET studies demonstrating that DA release in response to methylphenidate is attenuated in cocaine-addicted subjects relative to nonaddicted controls.⁷⁴ Presumably, the

cocaine stimulus is a more novel stimulus to nonaddicted subjects compared to cocaine-addicted volunteers. In an attempt to bridge these various roles of mesolimbic DA response, Salamone and colleagues³⁴ have suggested that NAc DA is a “sensorimotor integrator” that “is involved in higher order motor and sensorimotor processes that are important for activational aspects of motivation, response allocation, and responsiveness to conditioned stimuli”—which, the authors acknowledge, “may not roll off the tongue as fluently as the word ‘reward.’”

The role of the mesolimbic pathway, and particularly the NAc, is therefore more complicated (and more contentious) than previously believed. Nevertheless, a common characteristic of the above constructs may be taken to suggest that the mesolimbic dopamine system mediates the interpretation or learning of prospective positive and negative reinforcers, and that DA signaling appears to promote goal-directed behaviors regardless of the reinforcer type. More specifically, the mesolimbic system assesses the salience, or value, of a potential reinforcer. To make this assessment, other cortical and limbic brain regions must work concurrently with the brain reward circuitry. An understanding of the role of the addictive process therefore also requires the inclusion of brain regions neuronally connected to the VTA and NAc. As noted earlier, the VTA provides dopaminergic innervation not only to the NAc, but also to the amygdala and BNST. In addition, the VTA projects DA from a third dopaminergic tract, the mesocortical pathway, which innervates prefrontal cortical regions that include the orbitofrontal cortex (OFC) and anterior cingulate.¹¹ Coupled with glutaminergic and other reciprocal neurotransmitter connections, the NAc is integrated with the OFC, anterior cingulate, insular cortex, and hippocampus. Because of the importance of these regions in understanding the addictive processes discussed below, a brief description and diagram of these brain areas are provided in the text box and Figure 1.

How, then, does this new understanding of the mesolimbic dopamine pathway, and the inclusion of other limbic and prefrontal cortical regions, guide us in our understanding of the addictive process? The progression from initial drug use to addiction may evolve as repeated activation of the mesolimbic pathway associated with persistent drug use heightens the incentive value, or salience, of the drug. As contextual cues become associated and strengthened with repetitive drug administration, a process initially under the purview of the mesolimbic DA system progressively incorporates the neurocircuitry involved in emotional memory, obsessive thoughts, stress response, decision making, and behavioral inhibition into the drug experience. These neuroadaptive responses remain engaged even in the absence of ongoing drug use and are thought to be a primary factor in drug relapse. The following two sections will discuss the brain mechanisms

Brain Areas Involved in Addiction

Amygdala: Amygdalar activity is related to memory consolidation for emotionally arousing events. The amygdala is involved in assigning a reward value to stimuli and in the conditioning of fear to novel stimuli. For example, rodents favoring a specific cage that is identified with drug administration will lose this conditioned stimulus if the amygdala is ablated.

Anterior cingulate: Implicated in human disorders of emotion and attention, the anterior cingulate is involved in emotional self-control, focused problem-solving, error detection, performance monitoring, and adaptive response to changing conditions.⁷⁵ It plays a role in the detection of processing conflicts, particularly when low-frequency responses are executed,⁷⁶ but is influenced by both motivation and affective state.

Bed nucleus of the stria terminalis (BNST): Involved in autonomic and behavioral reactions to fearful stimuli, including the stress response, the BNST is considered part of the extended amygdala and shares with the nucleus accumbens a sensitivity to dopamine stimulation. In rats, the BNST is involved in the reinstatement of cocaine seeking after foot shock.⁷⁷

Dorsolateral prefrontal cortex (DLPFC): Implicated in difficulties holding/maintaining several pieces of information “on line” or in short-term storage (i.e., “working memory”), the DLPFC is crucial for the control and regulation of cognitive activities, including the sequencing of events, planning, and the selection of goals.

Hippocampus: Critical for the acquisition of new factual information and the formation of new memories about personally experienced events (i.e., episodic memory), the hippocampus has been implicated in the loss of memory in Alzheimer’s disease. Damage to the hippocampus results in anterograde amnesia and, to a lesser degree, in retrograde amnesia.

Insular Cortex: Important for the processing of pain, the insular cortex receives visceral, olfactory, gustatory, and other somatosensory inputs. It probably plays an important role in relating interoceptive signals to information from other modalities, and often shows activation in neuroimaging studies producing acute anxiety.

Orbitofrontal cortex (OFC): In addition to being implicated in disorders of impulsivity and decision making, the OFC is involved in situations that are unpredictable or uncertain, and modulates the reinforcement value of stimuli in the context of recent experience. It assesses and decodes the likely value or behavioral relevance of available choices of action and is therefore activated when there is insufficient information available to determine an appropriate course of action. Recent evidence suggests that the medial OFC (ventromedial cortex), with connections to the hippocampus and cingulate, is involved in assessing the familiarity or “rightness” of a situation and in integrating outcome expectancies. The lateral OFC, with connections to the amygdala and insula, is associated with the suppression of previously rewarded responses and is required to change behavior (i.e., to provide “stop” signals).⁷⁸

involved in the return to drug use, including the compulsive drug drive and the inhibitory dyscontrol observed in drug-addicted subjects, as well as the relationship of drug drive and inhibitory dyscontrol to dopaminergic dysregulation.

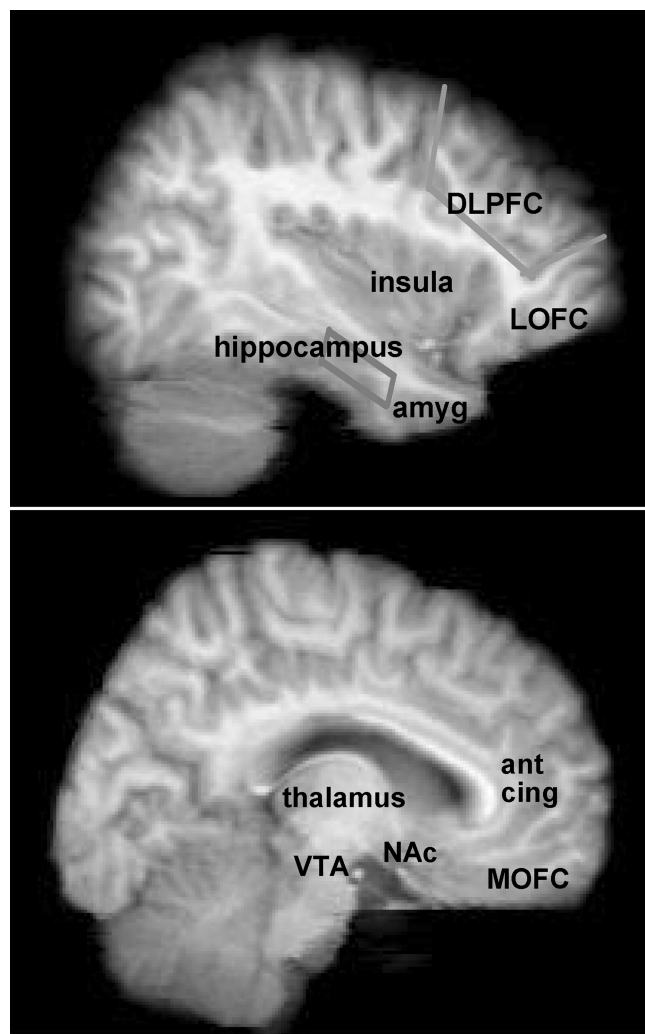


FIGURE 1. Brain regions relevant to the addictions (see text box for description of regions). Right panel represents an MRI of the sagittal brain (from SPM96) at Talairach coordinates $x=4-16$; left panel, at $x=34-46$. Each Talairach coordinate represents a one mm MRI sagittal slice, and 13 slices were averaged for each displayed image. Amyg, amygdala; ant cing, anterior cingulate; DLPFC, dorsolateral prefrontal cortex; LOFC, lateral orbitofrontal cortex; MOFC, medial orbitofrontal cortex (ventromedial cortex); NAc, nucleus accumbens; VTA, ventral tegmental area. The MRI template was obtained from SPM96-MRI.

THE COMPULSIVE DRIVE TO RELAPSE

Compulsive drug use can be conceptualized (adapted from Koob & Moal)³ as arising from four overlapping brain regions or pathways, each delineating a distinctive pull toward substance use. The four regions/networks coincide with common inducements for relapse: (1) priming (i.e., a single drink that precipitates a binge),⁷⁹ (2) drug cues, (3) craving,

and (4) stress. The sections on priming and drug cues also describe intracellular mechanisms involved in addictive processes.

Priming: The Nucleus Accumbens and Dopamine

Preclinical studies of priming confirm clinical observations—that a single drug administration is the most potent stimulus to renew drug use. Dopamine appears to play a critical role in priming, since the reinstatement of both opiate- and stimulant-seeking behaviors is elicited by the administration of directly acting dopaminergic agonists, and the priming effect of heroin, amphetamine, and cocaine is blocked by DA antagonists.⁵⁸ (Reinstatement refers to the reinitiation of drug seeking in animal models after the extinction of previous drug administration. See the review by Shaham and colleagues).⁸⁰ The effect of extracellular release of DA into the NAc upon drug-use behavior, however, is complicated by the heterogeneous responses of DA receptor subtypes. Dopaminergic receptors consist of two broad families (D1 and D2) and five subtypes (D1-like: D1, D5; D2-like: D2, D3, D4).⁸¹ Although both D1 and D2 agonists have reinforcing properties, the two receptors have distinct effects upon drug reinstatement. Stimulation of D2 receptors in the NAc induces drug-triggered relapse, whereas drugs that stimulate D1 receptors block drug-triggered relapse (see Self & Nestler⁵⁸ for review). The differences between D1- and D2-like receptors can be best understood through an appreciation of the postreceptor perturbations induced by drug-induced neurotransmitter release upon second messenger pathways. D2 receptors inhibit intracellular adenylyl cyclase by coupling with inhibitory G proteins that reduce cAMP production, whereas D1 receptors stimulate cAMP formation by activating membrane G proteins stimulating adenylyl cyclase. The chronic exposure to cocaine, heroin, morphine, and ethanol all induce an upregulation of the NAc cAMP second messenger pathway, with resultant increases in adenylyl cyclase and, in turn, protein kinase. Thus, it appears that relatively persistent D2-induced reductions in intracellular cAMP following chronic drug administration may result in increased drug self-administration, whereas these effects can be opposed by stimulation of D1 receptors.

D2 receptor ligands have not proven useful in the treatment of stimulant dependence; D2 receptor agonists are reinforcing in animal models, and D2 receptor antagonists are not effective in human studies. However, since D2-agonists appear to be especially potent in the induction of priming, medications targeting D2-like D3 and D4 receptors have been explored. In addition, whereas D1 and D2 receptors are more diffusely concentrated throughout the brain, D3 receptors are preferentially expressed in the mesolimbic system, particularly in the NAc, and D4 receptors have their highest

densities in the prefrontal cortex (PFC) and suprachiasmatic nucleus of hypothalamus.¹¹ Preclinical studies reveal that D3 receptor antagonists block both cocaine's reinforcing actions and cocaine-induced reinstatement of cocaine-seeking behaviors;^{82,83} a partially selective D3 receptor ligand is now undergoing assessment for human trials.⁸⁴ In an exciting human study assessing the interaction between genetic factors and drug use, healthy subjects with different D4 variable-number-of-tandem-repeats (VNTR) polymorphisms were administered a priming dose of alcohol and then assessed for craving. Groups with different D4 VNTR polymorphisms demonstrated a differential response to the D4 antagonist,⁸⁵ portending the developing importance of pharmacogenetics to inform the targeted use of medications based upon an individual's genotype.

Drug Cues: The Nucleus Accumbens and Amygdala

The power of drug-related cues to induce a return to drug use is routinely observed in the clinical setting, prompting the admonition for addicted patients to avoid the "people, places, and things" that have been associated with their drug use. (Although such cues can induce craving, this phenomena is discussed in the following section). Di Chiara¹⁵ posits that the repeated use of drugs strengthens both stimulus-response and stimulus-reward associations, thus sensitizing the mesolimbic pathway and internally linking the association between the substance and its associated drug cues. The imbedding of the experience of substance use in tandem with the attendant conditioned environmental stimuli produces an "addiction memory"⁸⁶ or "neural ghost" (Glenn Horwitz, personal communication). This neural ghost remains imbedded in the mesolimbic circuitry, particularly the amygdala⁸⁷—often outside of conscious awareness. Upon stimulation of the mesolimbic pathway, either by conditioned drug cues⁸⁸ or by drug priming, the circuit is activated, inducing a desire, or wanting, for additional drug.

The amygdala is implicated in the acquisition, storage, and expression of emotional memories. PET and fMRI neuroimaging studies of cocaine^{89–92} and nicotine-addicted subjects⁹³ show that cue exposure to drug-associated stimuli induces an activation of the amygdalar region. When animals are trained to associate a specific "place" with drug administration (i.e., conditioned place preference), they tend to return to the environment associated with receiving the drug. Following ablation of the amygdala, the animals "forget" this association.^{94,95} The reinforcing effect of the drug remains, however, as drug self-administration persists following amygdalar ablation. The formation of the associations between salient stimuli and internally rewarding (or aversive) events is facilitated by stimulation of dopaminergic neurons.⁴⁹ However, glutamate also appears to be a primary mediator of cue-induced behavioral plasticity via

glutamatergic connections that project from the amygdala to the NAc.⁹⁶ The increase in glutamate release following repeated cocaine administration also mediates, at least in part, cocaine-induced sensitization.^{97,98}

A relatively new area of investigation explores the intracellular mechanisms that accompany repeated drug use, positing that the mnemonic connections that underlie cue-induced relapse are mediated by relatively long lasting cellular and molecular adaptations. The extracellular release of neurotransmitters can induce these alterations in intracellular processes by increasing or decreasing protein synthesis, including messenger, transcription, and scaffolding (or structural) proteins. Messenger (e.g., G) proteins were discussed in the previous section. Transcription factors regulate mRNA gene transcription by binding to the regulatory regions of specific genes. The two transcription factors most strongly associated with the chronic drug administration are Δ FosB and CREB (cAMP response element-binding protein) (see Nestler⁹⁹ and Chao & Nestler¹⁰⁰ for reviews). Δ FosB is a member of the Fos family of immediate early gene transcription factors. Most and possibly all members of this family are rapidly induced after the acute exposure to amphetamine, cocaine, ethanol, nicotine, opiates, and PCP. Δ FosB is unique among these proteins in that it is very stable and persists intracellularly for several weeks or months.¹⁰¹ The repeated administration of drugs therefore results in an accumulation of Δ FosB, primarily in striatal GABAergic medium spiny neurons containing dynorphin and substance P.^{102,103} Δ FosB decreases the expression of dynorphin in these striatal projection neurons. The drug-induced accumulation of Δ FosB enhances sensitivity to the rewarding effects of cocaine and morphine,^{103,104} possibly due to the feedback effect of striatal dynorphin upon kappa-opioid receptors on VTA dopaminergic neurons. Since the uniquely stable Δ FosB also accumulates in the amygdala and PFC, it has been suggested that Δ FosB may be the "molecular switch" that retains the connection between the experience of drug reward and the drug-associated cues long after drug use has ceased.¹⁰⁵

The Obsessive Drive for Drugs: The Striato-Thalamo-Orbitofrontal Circuit

The pathway involved in the compulsive drive for substances is the striato-thalamo-orbitofrontal circuit. This circuit is tightly interconnected with other prefrontal and limbic regions, including the anterior cingulate, insula, dorsolateral prefrontal cortex (DLPFC), and amygdala. Innervation includes both the mesocortical dopaminergic pathway, which projects to PFC regions that include the OFC and anterior cingulate,¹¹ and glutamate neurons that project reciprocally between the PFC and amygdala, as well as from the PFC to the NAc and VTA.⁹⁶ This striato-thalamo-orbitofrontal circuit has been implicated in obsessive-compulsive disorder

(OCD), a syndrome sharing common features with the addictive disorders; that is, the drive for drugs and alcohol includes a lack of control over intrusive thoughts and compulsive behaviors that are directed toward obtaining and administering substances.^{106,107}

The obsessive-compulsive nature of substance use can be empirically assessed with the Obsessive Compulsive Drinking Scale,¹⁰⁶ a predictive measure of treatment outcome.¹⁰⁸ Single photon emission computerized tomography (SPECT) and PET imaging studies demonstrate increased activation of the OFC, anterior cingulate, and striatum in OCD, and this brain activity normalizes following successful pharmacologic or psychosocial treatment.^{109–111} Heightened activation of the OFC is similarly observed in cocaine-addicted subjects during cocaine craving¹¹² and both procaine¹¹³ and methylphenidate¹¹⁴ administration, suggesting that the OFC is hypersensitive to a variety of psychological and pharmacologic challenges. In addition, other PET^{90–92,114} and fMRI^{112,115,116} studies during craving for cocaine, methylphenidate, and alcohol have demonstrated activation of the anterior cingulate, DLPFC, insula, and amygdala. Garavan and colleagues,¹¹⁷ however, compared regional brain activation with fMRI in cocaine-addicted and nonaddicted subjects while viewing films portraying individuals either smoking crack cocaine or engaged in sexual activity. The cocaine cues activated similar neuroanatomical substrates as the natural (sexual) stimuli in the cocaine-addicted subjects, suggesting that activation of these cortical and limbic regions may not be associated with a dedicated circuitry specific to drug cues. Of particular interest, however, was the finding that, whereas the cocaine-addicted subjects reacted more strongly to the cocaine cues than controls (as expected), the cocaine-addicted group showed an attenuated brain signal in response to the sexual stimuli relative to the nonaddicted group. Consistent with clinical observations, this study implies that persistent drug use induces “wanting” only in response to drug-related cues—and not in response to natural cues. The chronic use of drugs therefore appears to co-opt higher-order neuronal circuitry, such that executive functioning responds primarily to drug-related stimuli and that planning, decision-making, and attentional processes all subserve drug acquisition and ingestion.

Stress-Induced Relapse: The Limbic-Hypothalamic-Pituitary-Adrenal Axis

Stress is a common precipitant of relapse in addicted patients,¹¹⁸ and intermittent stress is a powerful inducer for the reinstatement of substance use in animal models.^{58,119} Preclinical studies investigating this phenomena have revealed that stressors (including defeat stress, intermittent shock, maternal separation, prenatal stress, social isolation, tail pinch, unstable social environment, and food depriva-

tion or restriction) are all important modulators of drug-seeking behavior, although the effect on any specific stressor is stressor-, procedure-, and drug-specific. Intermittent foot shock, however, tends to be the most consistent stress inducer of drug reinstatement (see Lu et al.¹¹⁹ for review). The stress circuit includes the hypothalamic-pituitary-adrenal (HPA) and extrahypothalamic corticotropin-releasing factor (CRF) stress systems, including the amygdala and BNST.³ External stressors stimulate a return to drug use through the BNST⁷⁷ and amygdala,⁵⁸ regions that are particularly sensitive to the anxiogenic effects of the neuropeptide CRF. Reinstatement to drug use following foot shock is blocked by the administration of CRF antagonists,¹²⁰ revealing that CRF is a mediator in this relapse process. Norepinephrine (projecting from the locus coeruleus)^{121,122} and glutamate (projecting from the amygdala)¹²³ are also involved in the stress-induced reinstatement of drug use. As described with drug-related cues and craving, reinstatement induced by foot shock likewise involves glutaminergic projections from the PFC and amygdala to the NAc.¹²³

Stress interacts with mesolimbic DA through the peripheral release of glucocorticoids. Following stress-induced activation of the HPA axis, glucocorticoids cross the blood-brain barrier into the central nervous system and bind with VTA (and other) glucocorticoid receptors.^{124,125} Glucocorticoids have a permissive effect upon mesolimbic DA,^{126,127} and both stress and substances of abuse (e.g., amphetamine, cocaine, ethanol, morphine, and nicotine) cause a similar excitation of midbrain dopaminergic cells.¹²⁸ Thus, the stress-induced release of both extrahypothalamic CRF and the glucocorticoids stimulates neuronal pathways involved in the compulsive drive for substance use. Conversely, abstinent alcohol-dependent subjects demonstrate an attenuated responsiveness of the HPA axis in response to pharmacologic and psychosocial stressors.^{129–131} This “inverse U” pattern, in which both the paucity and excess of glucocorticoids can be deleterious, is observed in a wide range of physiologic functions.¹³² Since preliminary studies suggest that an attenuation of HPA-axis functioning predicts relapse following treatment,^{133,134} medications that increase HPA tone may be useful in the treatment of alcohol-addicted subjects. For example, the opioid antagonists naltrexone and nalme-fene block the inhibitory effect of the endogenous endorphins on paraventricular corticotropin-releasing hormone (CRH),^{135,136} thereby increasing corticotropin and cortisol. Opioid antagonists may subsequently decrease relapse by easing alcohol-related suppression of the HPA axis, resulting in normalization of the HPA-axis response to stress.

In summary, four overlapping networks of dopaminergic and glutaminergic projections integrate the brain regions mediating emotional memory, drug desire, and stress response with the primary repository of drug salience—that is, the VTA and NAc. Extracellular synaptic events induce

intracellular changes that may underlie the persistence of the drug-associated cues long after drug use has ceased. The divergent precipitants of drug relapse and their associated extra- and intracellular perturbations suggest that pharmacologic interventions for drug relapse must intervene in multiple neuronal circuits, possibly targeting specific pathways for individual drive states.

INHIBITORY DYSCONTROL OF THE COMPULSIVE DRIVE STATE

The compulsive drug drive cannot fully account for recurrent relapse. Despite an enduring desire for alcohol or drugs, a sizable percentage of addicted patients maintain a lifetime of abstinence. The slip-induced relapse, the cue-induced cravings, the obsessive thoughts, and the return to drug use following traumatic events can be thwarted by a robust inhibitory control over the compulsive drive state. A deficit in inhibitory restraint (i.e., impulsivity), however, can provide a window through which the drive for drugs can express itself. Even in the absence of a compulsive drug drive, the relative absence of inhibitory control may lead to spontaneous drug use (see Figure 2). The relative absence of inhibitory restraint in addicted subjects is observed in standardized and experimental neurocognitive measures of impulsivity and decision making,^{137–142} revealing deficits in the ability of addicted subjects both to inhibit prepotent (or powerfully habituated) responses¹³⁷ and to choose greater delayed rewards over lesser immediate ones.^{138,141,142}

The OFC is critically involved in assessing the salience of potential rewards and punishments (i.e., high vs. low monetary rewards, immediate vs. delayed gain, similar or dissimilar objects) and is involved in both impulsivity and

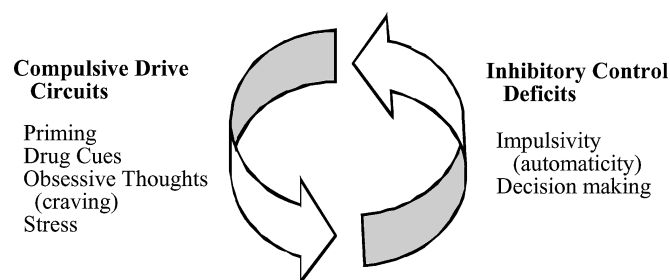


FIGURE 2. The compulsive drive toward drug use describes relapse in response to a priming dose of drug, drug cues, craving, or stress. These triggers for a return to drug use are mediated by overlapping brain regions/circuits: mesolimbic (priming), mesolimbic and amygdala (drug cues), striato-thalamo-orbitofrontal (obsessive thoughts), and extrahypothalamic CRF and the HPA axis (stress). A deficit in inhibitory control and poor decision making, mediated in part by the OFC cortex and anterior cingulate, may result in relapse even in the absence of a compulsive drug trigger. Adapted from Koob & Moal³ and Jenstch & Taylor.¹⁷

decision making. Patients with lesions of the OFC, for example, make irresponsible and impulsive decisions, yet their intellectual abilities—such as memory, learning, language, and attention—are often preserved. In general, there appears to be a perseveration of behavior, with continued responding to stimuli that are no longer rewarding; a reversal of reinforcement contingencies does not reverse behavioral responses.¹⁴³ For example, subjects with lesions of the OFC perform poorly on the Gambling Task,¹⁴⁴ which simulates real-life experiences involving uncertainty, reward, and punishment. Several investigators have demonstrated that drug- and alcohol-addicted subjects perform poorly on this task.^{142,145,146} Another key region involved in inhibitory restraint is the anterior cingulate, which monitors performance, detects conflicts, and assesses emotional self-control. Performance on the Gambling Task is highly correlated with resting rCBF of the anterior cingulate.¹⁴⁷

Using PET imaging techniques, Volkow and colleagues have demonstrated a strong correlation between striatal D2 receptor number and energy utilization of the OFC and anterior cingulate in cocaine-³⁶ and methamphetamine-addicted¹⁴⁸ patients. The lower the number of D2 receptors, the lower the activity of the OFC and anterior cingulate. The decrease in basal OFC regional cerebral blood flow (rCBF) in cocaine-addicted subjects, relative to controls, has been confirmed in our laboratory using SPECT imaging techniques (see Figure 3).¹¹³ The correlation between D2 receptor number and OFC and anterior cingulate activity reported by Volkow and colleagues^{36,148} may suggest a neurobiologic connection between the compulsive drive state and the inhibitory deficit associated with drug addiction. Thus, a similar alteration in the mesocortical pathway may concurrently produce an impaired inhibitory control (due to decreased mesocortical input into the PFC) over a heightened desire for drug-induced stimulation (due to an attenuated response to natural reinforcers associated with the reduction in striatal D2 receptors).

Brain regions involved in the inhibitory processes, particularly the OFC and the anterior cingulate, have therefore been the focus of several neuroimaging studies of subjects with substance use disorders. As noted above, both PET and SPECT studies have shown that abstinent cocaine-,^{36,113} alcohol-,¹⁴⁹ and methamphetamine-addicted¹⁵⁰ subjects demonstrate decreased basal activity in the OFC. During the Stroop Interference Task, which assesses the ability to inhibit a prepotent response (i.e., response inhibition), the relationship between task performance and OFC activation is disrupted in cocaine- and alcohol-addicted subjects.¹⁵¹ OFC activation, as assessed by fMRI, is also muted in a decision-making task in methamphetamine-addicted subjects.¹⁵² The anterior cingulate shows decreased activation in addicted subjects during a task of response inhibition,¹⁵³ procaine administration,^{113,154} and script-guided stress induction.¹⁵⁵

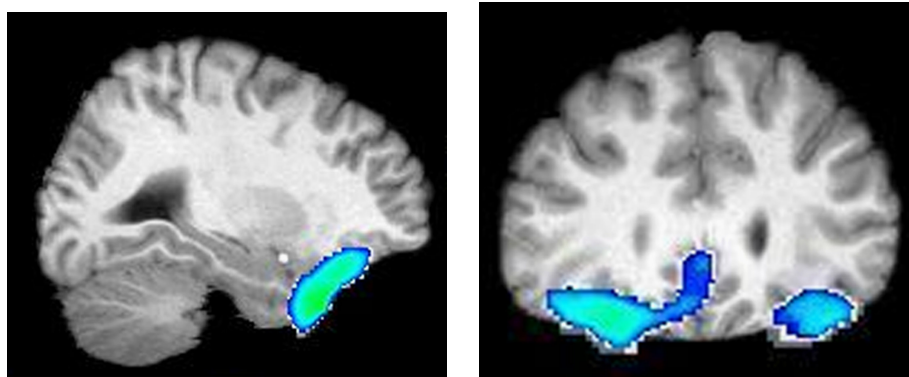


FIGURE 3. Decreased blood flow in the medial and lateral orbitofrontal cortex may contribute to the deficits in inhibitory control observed in addicted subjects. The figure demonstrates decreased rCBF ($p < 0.01$, in blue) in the orbitofrontal cortex of 37 two- to four-week abstinent cocaine-dependent men and women relative to 36 age-matched controls. Sagittal view (left panel) is at Talairach coordinate $x = 28$; coronal view (right panel), at $y = 30$ (right is to reader's left). From Adinoff and colleagues, unpublished data.

Impaired functioning of the OFC^{156,157} and the anterior cingulate, particularly in response to cognitive tasks engaging either inhibitory processes or decision making, suggests that these brain areas may be involved in the addict's inability to appropriately restrain the drive toward relapse.

The OFC and anterior cingulate also play a prominent role in the obsessive thoughts and craving described earlier. However, whereas these brain regions demonstrate increased regional brain activation (relative to controls) during craving induction, they generally show decreased activation (relative to controls) during other activating tasks (see above). These findings suggest that the mesocorticolimbic pathway does not appropriately engage non-drug-related cognitive or emotional stimuli, but is hyperresponsive to drug-related cues.

FUTURE DIRECTIONS: MEDICATION DEVELOPMENT

This review has described the progressive elucidation of neurobiologic mechanisms underlying uncontrolled drug use, focusing on the distinctive role that dopamine plays in reward and addiction. The ultimate aim of these efforts is to guide medication development for the addictive disorders. Several potential targets have been mentioned, with a focused intervention upon dopaminergic receptors. The review highlights the importance of the mesolimbic pathway in the development of an addiction—which thus may be an optimal site for intervention early in the addictive process. In high-risk individuals (i.e., those with strong genetic or environmental risk factors for the development of a substance use disorder), medications interacting with the mesolimbic pathway to decrease the incentive salience of drugs may even prove useful as a preventive measure. By contrast, in the case of

repetitive drug use—which engages the prefrontal regions—the mesocortical pathway may be a more appropriate target for treatment. The review notes the relative importance of various types of triggers, and as mechanisms are developed to isolate the particular relapse style of an individual patient, targeted interventions (both psychosocial and pharmacologic) can be directed toward the trigger-relevant neurotransmitter system and neuronal circuit. For example, addicted patients who report an intense response to specific cues may best respond to disruptions in amygdalar-mesolimbic connections, whereas a patient identified as an impulsive relapser¹⁵⁸ may require improved efficiency of orbitofrontal or anterior cingulate functioning—possibly by intensifying dopaminergic input. Isolating genotypes should lead to a pharmacogenetic approach to drug development, offering a specific drug treatment appropriate to an identified genetic polymorphism. Finally, drug-induced postsynaptic alterations in structural,¹⁵⁹ messenger, and transcription proteins offer an exciting focus for future medication targets. In addition to the previously discussed prospective medications, dopaminergic agents presently being assessed include vanoxerine,^{160,161} a long-acting, noncompetitive inhibitor of the presynaptic DAT, and disulfiram, which inhibits dopamine-B-hydroxylase.¹⁶²

Other receptor systems directly synapse upon dopaminergic neurons and offer excellent possibilities for pharmacologic intervention. As noted early in the review, most drugs of abuse have high affinity binding with G protein-mediated or ion channel receptors that activate dopaminergic release. Pharmacologic manipulations of these receptor systems have proven of some utility in drug treatment, and several new approaches are in development. Naltrexone, for example, appears to decrease alcohol craving^{163,164} by blocking the mu-opioid receptors that suppress GABAergic neurons. These neurons, in turn, tonically inhibit VTA dopaminergic neurons.¹⁶⁵ Antagonism of mu-opioid receptors thus

results in the disinhibition of the GABAergic neurons, causing a net decrease in VTA DA release. Opioid antagonists seem to have little effect, however, on the craving for other substances, including heroin. Baclofen, a GABA_B receptor agonist that inhibits dopamine release, reduces stimulant self-administration in preclinical studies¹⁶⁶ and has shown early promise in reducing cocaine use in human studies.¹⁶⁷ Early suggestions of clinical efficacy in cocaine-dependent subjects have also been reported with vigabatrin, a selective, irreversible inhibitor of GABA transaminase.¹⁶⁸ Enadoline, which binds to kappa-opioid receptors and inhibits DA release, attenuates the neurochemical and behavioral effects of cocaine in preclinical studies and is being assessed for human trials.¹⁶⁹ Topiramate both facilitates GABA functioning through a non-benzodiazepine site on the GABA_A receptor and antagonizes glutamate activity at the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate receptors. This compound has demonstrated efficacy in both alcohol-¹⁷⁰ and cocaine-dependent¹⁷¹ subjects. Glucocorticoid antagonists or agonists may prove useful by altering the permissive effects of mesolimbic DA release, particularly during periods of stress. Metyrapone, which blocks the synthesis of cortisol, is currently being assessed for cocaine addiction in phase I clinical trials, although suppression of HPA-axis activity by ketoconazole has not been effective in decreasing cocaine use.¹⁷² As discussed previously, however, medications that activate, not inhibit, HPA-axis functioning may prove more beneficial. 5HT₃ receptors are abundant in central DA terminal areas, such as the NAc and striatum, and appear to mediate the excitatory effect of compounds acting upstream from DA neurons.¹⁷³ Altering 5HT₃ transmission with the 5HT₃ antagonist ondansetron inhibits cocaine-induced sensitization,¹⁷⁴ decreases alcohol use in early-onset alcohol-dependent subjects,¹⁷⁵ and is being evaluated in phase II clinical trials for cocaine dependence.¹⁷⁶ Cannabinoids activate mesolimbic DA through the CB₁ receptor, and the CB₁ receptor antagonist rimonabant decreases cocaine reinstatement.¹⁷⁷ Whereas DA increases appetitive behavior, cholinergic agonists inhibit appetitive behavior and increase avoidance behavior.¹⁷⁸ Behavioral reinforcement has therefore been envisioned as a balance between NAc DA and the cholinergic system¹⁷⁹—mediated, at least in part, by cholinergic interneurons within the NAc. Preclinical studies have demonstrated an inhibitory effect of cholinergic agonists on cocaine self-administration.^{180,181} Ibogaine, a naturally occurring indole alkaloid, binds to kappa-opioid, NMDA glutamate, and nicotinic receptors, and blocks the expression of NAc DA in cocaine-sensitized animals.¹⁸² Ibogaine has been shown to decrease cocaine, ethanol, morphine, and nicotine self-administration in animal models,¹⁸³ and extensive anecdotal evidence suggests this drug has treatment efficacy in cocaine and heroin addiction.¹⁸⁴ Several of these new approaches are being tar-

geted by the National Institute on Drug Abuse's Clinical Research Efficacy Screening Trial.¹⁷⁶

Experience with other chronic medical and psychiatric disorders, such as depression, epilepsy, hypertension, and schizophrenia, suggest that a cocktail of pharmacologic interventions will be required for the successful treatment of many addicted individuals. Medications targeting multiple receptor systems and designed for an individual's specific relapse characteristics, genotype, and addiction severity may be the optimal intervention as medication development progresses.

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